I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On January 5, 2007

TOWNSEND and TOWNSEND and CREW LLP

By: [signature]

PATENT
Attorney Docket No.: 02307O-067720US
Client Ref. No.: 96-215-3

OIPE JAN 08 2007 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5513
LALEH SHAYESTEH et al.	Examiner: Jehanne Souaya Sitton
Application No.: 08/905,508	Technology Center/Art Unit: 1634
Filed: August 4, 1997	DECLARATION UNDER 37 CFR 1.132
For: GENETIC ALTERATIONS ASSOCIATED WITH CANCER	
Customer No.: 20350	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Joe W. Gray, am a Professor of Laboratory Medicine and Radiation Oncology at the University of California San Francisco. I am a co-inventor of the subject matter disclosed and claimed in the above-referenced patent application.

2. I received a Ph.D. in Physics in 1972 from Kansas State University. My field of expertise is cancer and cytogenetics. I have been in this field for over 30 years and have authored over 300 publications in this area.

3. I have read and am familiar with the contents of the above-referenced patent application and claimed subject matter. I understand that the Examiner has rejected the current claims as allegedly unpatentable over the combination of the prior art teachings of Bonjouklian, *et al.* (U.S. Patent No. 5,378,725, "Bonjouklian") in view of Arnold, *et al.* (*Genes, Chromosomes, and Cancer* 16:46-54, 1996, "Arnold") and Volinia, *et al.* (*Genomics* 24:472-477,

1994, "Volinia") and further in view of Xiao, *et al.* (*International Journal of Oncology* 6:405-411, 1995, "Xiao") or alternatively, Skorski, *et al.* (*Blood* 86:726-736, 1995, "Skorski"). In particular, it is my understanding that the rejection is based on the following arguments.

4. Bonjouklian is characterized by the Examiner as describing administration of a phosphatidyl inositol 3 (PI3) kinase inhibitor, *e.g.*, wortmannin, to treat a PI3 kinase-dependent condition such as abnormal cell growth in a neoplasm such as ovarian cancer. Arnold is described in the rejection as teaching an increase in copy number of 3q26-qter in ovarian tumors. The Examiner alleges that it would have been obvious to one of ordinary skill in the art at the time of the invention to detect amplification of the gene encoding the catalytic subunit of PI3 kinase, *i.e.*, *PIK3CA*, in ovarian cancer cells in a patient and to administer the PI3 kinase inhibitor wortmannin. Specifically, the Examiner contends that it would have been obvious because Arnold teaches that 3q26-qter is amplified in 42% of ovarian tumors that they analyzed and the *PIK3CA* gene is found at 3q26.3 (as taught by Volinia); and Bonjouklian teaches administration of a PI3 kinase inhibitor. The Examiner cites Xiao and Skorski as teaching that wortmannin inhibits proliferation of gastric cancer cell lines that overexpress PI3 kinase and of leukemia cells that require PI3 kinase for proliferation. It is the Examiner's position that Xiao and Skorski provide a basis for expecting that wortmannin treatment of ovarian cancer cells, as allegedly suggested by Bonjouklian, would inhibit proliferation.

5. This declaration is provided to show that the fact that the broad region of 3q26-qter was known to be amplified in ovarian cancer would not lead one of skill in the art to conclude that amplification of *PIK3CA*, which is one of numerous genes located in this broad region, leads to overexpression of PIK3CA and is therefore indicative of a role for PI3 kinase in oncogenesis in ovarian cancer cells that contain the amplified region.

6. Arnold describes a comparative genomic hybridization (CGH) study of forty nine ovarian cancer tumors. In this CGH analysis, differentially labelled total genomic DNA from a tumor sample and from a normal reference control sample were co-hybridized to normal metaphase chromosomes. The resulting ratio of the fluorescence intensities of the probes hybridized to the chromosomes is approximately proportional to the ratio of the copy numbers of the corresponding DNA sequences in the tumor and normal reference genomes. Arnold

identified the region of 3q26-qter as being increased in copy number in 42% of the ovarian tumors that were analyzed. However, although it was known in the art that the gene encoding the catalytic subunit of PI3 kinase (PIK3CA) is located at 3q26.3, the CGH study as performed by Arnold using metaphase chromosomes does not provide sufficient resolution to determine that the chromosomal subregion containing the PIK3CA locus is a focal point of amplification.

7. Furthermore, even though a gene may be present in an amplified chromosomal region, that fact alone does not lead one of skill to conclude that a particular gene is overexpressed. Many genes are present in chromosomal region 3q26-qter. For example the genome browser of the University of California, Santa Cruz (http://genome.ucsc.edu/cgi-bin/hgTracks?hgsid=83748260&clade=vertebrate&org=Human&db=hg18&position=3q26&pix=620&Submit=submit&hgsid=83748260, a print out of which is attached hereto, shows that numerous genes are located in the 3q26 region alone; however, there is no evidence that all or most of the products of these many genes are overexpressed in ovarian tumors.

8. It is my opinion as one who has practiced in this art for many years that although *PIK3CA* may have been identified as a potential gene of interest in the 3q26-qter region identified by Arnold due to its biological function in proliferation or its overexpression in other cancers, at the time of the invention one of skill could not have concluded that the mere presence of the gene in this broadly amplified region would predictably lead to a correlation with overexpression of the protein and an oncogenic role in ovarian cancer cell proliferation.

9. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon.

Dated: ____________ ____

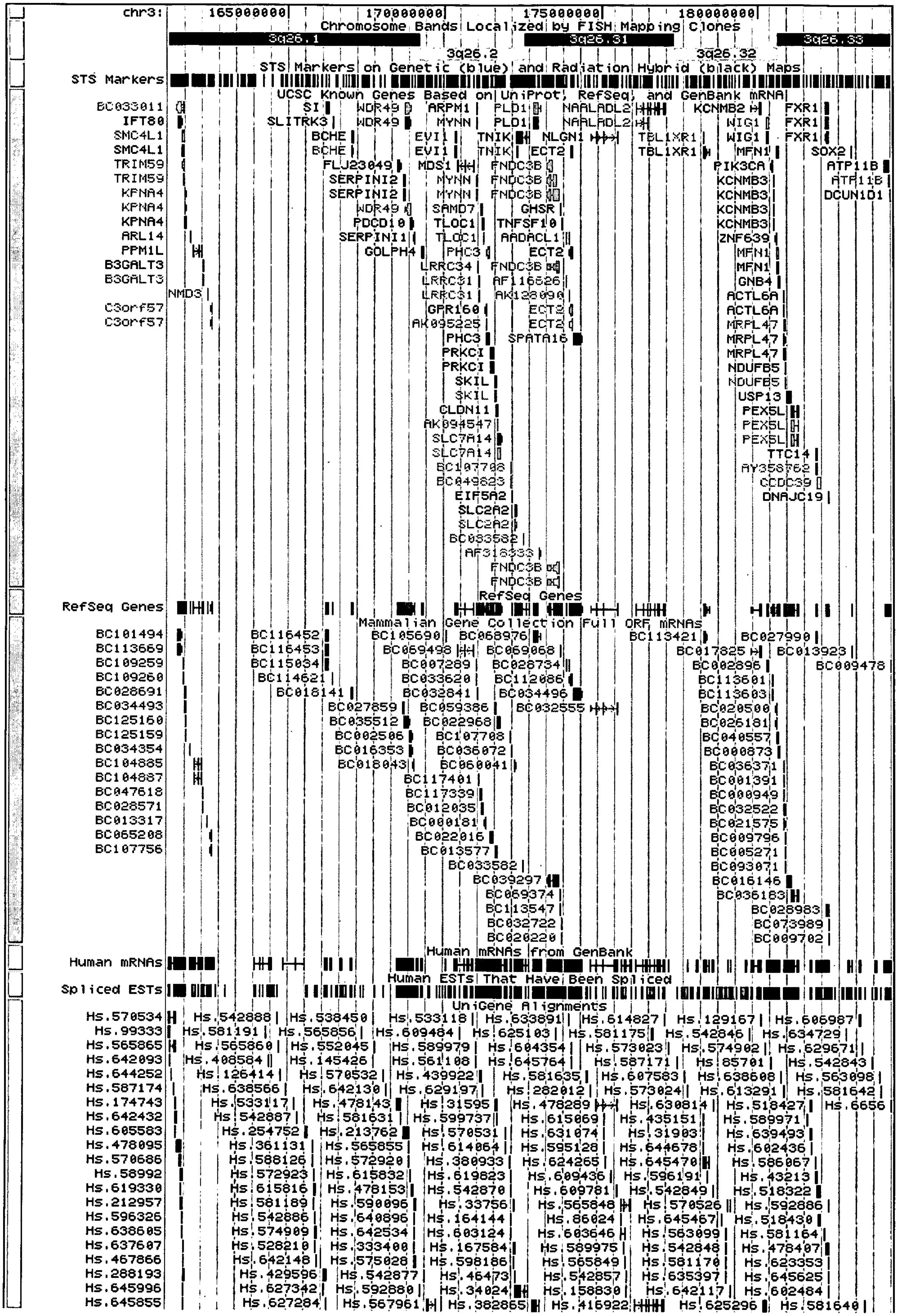
Joe Gray, Ph.D.

Home Genomes Blat Tables Gene Sorter PCR DNA Convert Ensembl NCBI PDF/PS Help

UCSC Genome Browser on Human Mar. 2006 Assembly

move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x

position/search chr3:161,200,001-184,200,000 jump clear size 23,000,000 bp. configure



BEST AVAILABLE COPY

move start < 2.0 > Click on a feature for details. Click on base position to zoom in around cursor. Click on left mini-buttons for track-specific options. move end < 2.0 >

default tracks | hide all | add custom tracks | configure | refresh

Use drop down controls below and press refresh to alter tracks displayed.
Tracks with lots of items will automatically be displayed in more compact modes.

Mapping and Sequencing Tracks

Base Position dense	Chromosome Band pack	STS Markers dense	FISH Clones hide	Recomb Rate hide
Map Contigs hide	Assembly hide	Gap hide	Coverage hide	BAC End Pairs hide
Fosmid End Pairs hide	GC Percent hide	Short Match hide	Restr Enzymes hide	

Phenotype and Disease Associations

Locus Variants hide				

Genes and Gene Prediction Tracks

Known Genes pack	RefSeq Genes dense	Other RefSeq hide	MGC Genes pack	Ensembl Genes hide
AceView Genes hide	N-SCAN hide	SGP Genes hide	Geneid Genes hide	Genscan Genes hide
Exoniphy hide	Superfamily hide	EvoFold hide	sno/miRNA hide	

mRNA and EST Tracks

Human mRNAs dense	Spliced ESTs dense	Human ESTs hide	Other mRNAs hide	Other ESTs hide
H-Inv hide	UniGene pack	Poly(A) hide		

Expression and Regulation

Affy HuEx 1.0 hide	Allen Brain hide	GNF Atlas 2 hide	GNF Ratio hide	Bertone Yale TAR hide
Affy U133 hide	Affy GNF1H hide	Affy U133Plus2 hide	Affy U95 hide	CpG Islands hide
FirstEF hide	TFBS Conserved hide	ORegAnno hide	7X Reg Potential hide	

Comparative Genomics

Conservation pack	Most Conserved hide	Fugu Chain hide	Fugu Net hide	Tetraodon Chain hide
Tetraodon Net hide	Tetraodon Ecores hide	Zebrafish chain hide	Zebrafish Net hide	X. tropicalis Chain hide
X. tropicalis Net hide	Chicken Chain hide	Chicken Net hide	Opossum Chain hide	Opossum Net hide
Cow Chain	Cow Net	Dog Chain	Dog Net	Rat Chain

hide	hide	hide	hide	hide
Rat Net	Mouse Chain	Mouse Net	Rhesus Chain	Rhesus Net
hide	hide	hide	hide	hide
Chimp Chain	Chimp Net			
hide	hide			

Variation and Repeats

SNPs	Segmental Dups	RepeatMasker	Simple Repeats	Microsatellite
dense	hide	dense	hide	hide
Self Chain				
hide				

refresh